National Cancer Institute

An epidemiologic view of low dose ionizing radiation and cancer: Putting risk into perspective

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Space Weather Workshop, Boulder, CO—April 8, 2014

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

"And it was so typically brilliant of you to have invited an epidemiologist."

Questions

- What do we think we know about radiation-related cancer risk in humans?
- What are some basic principles in studying risk?
  - Relative and absolute risk (in simple terms)
  - Example from medical radiation studies (CT scans)
  - Learn about risk from different sources of exposure
- Why can't we directly measure cancer (or any) risk in humans at low radiation doses? Say, under 100 mGy?
  - Power (detecting "signal" above the background cancer rates)
  - Confounders (and uncertain measurement of confounders)
  - Uncertain radiation organ absorbed dose estimates
- How else to assess low dose risk?
  - Predictive human models of risk from "higher" to "lower" doses
  - Use intermediate endpoints, such as chromosome aberrations
- What do recent air crew studies show?
- Summary?

What we think we "know"

- Organs and tissues vary in their radiation sensitivity
  - Sensitive: Breast, brain, thyroid, bladder, ovary
  - "Resistant": Small intestine, prostate

- Radiation-related cancer risks decrease as age at exposures increases
  - Many studies have shown this

- Increased cancer risk persists indefinitely after radiation exposure
  - A-bomb survivors, childhood cancer survivors

- Radiation-related cancer risk is likely linear at low doses
  - Roughly defined as <100 mSv; linearity is highly controversial

- Some factors can markedly change the radiation-related cancer risk

Fitted breast cancer risk by radiation dose to the breast and ovary.
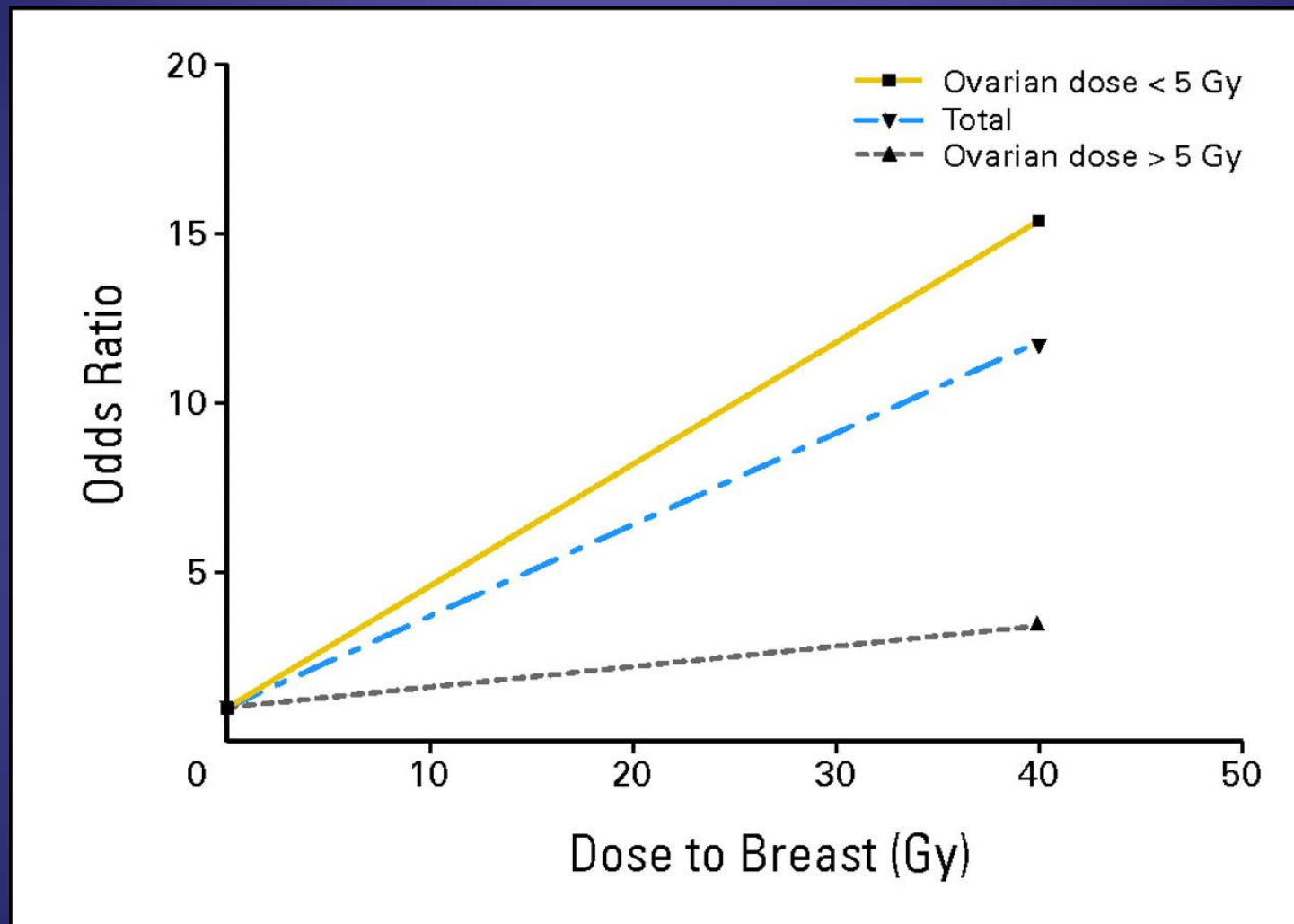
What are some basic principles in studying health risks in humans?

Methods to assess risk

- Case reports or series
  - Early etiologic clues

- Analytic studies (cohort or case-control)
  - Quantitative estimates of overall risk
  - Dose response and excess risks (ERR/Gy)
  - Collect information on other factors
    - Assess interaction (age at exposure, gender, smoking)
    - Control for confounders (age, gender, sun exposure)

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    - Assess interaction (age at exposure, gender, smoking)
    - Control for confounders (age, gender, sun exposure)
    - **A confounding factor must be related to the outcome and the exposure of interest.**

Measures of risk (1)

Relative Risk (multiplicative)

- Rates of disease in exposed divided by rates of disease in unexposed (cohort study, Rate Ratio)
- Odds of exposure in cases relative to the odds of exposure in controls (case-control, Odds Ratio)

Absolute Risk (additive)

- Number of excess cases of disease expected due to the exposure, expressed per unit of time
- Public health, risk/benefit, policy decisions

Measures of risk (2)

EXAMPLE:
Relative Risk and Absolute Risk

- Radiation exposure from CT scans in childhood and subsequent risk of leukemia and brain tumors: a retrospective cohort study
  - Pearce et al, Lancet 2012
  - ~178,000 under age 22 at time of CT scan
  - Followed over 1985-2008
  - England, Scotland and Wales
    - Nat'l Health Service records and GB cancer registry

Diagnostic Imaging - Effective & Organ Doses

Procedure	X-ray	CT scan
Skull	0.1 mSv	2 mSv
Chest	0.1 mSv	7 mSv
Abdomen	0.7 mSv	8 mSv

CT scan	Brain	Lung	Stomach
Skull	40 mGy	0 mGy	0 mGy
Chest	0 mGy	20 mGy	6 mGy
Abdomen	0 mGy	3 mGy	20 mGy

Mettler F et al (Radiology 2009)

Slide courtesy of Dr. Amy Berrington de Gonzalez

Comparing effective doses

- Airline pilots and flight crews
  - Flying 600-1000 hours per year
  - Annual effective dose 0.2-6mSv
    - » Friedberg and Copeland, 2003
  - Working lifetime cumulative effective dose
    - On average, 10-30 mSv
    - Rarely over 80 mSv
      - » Hammer et al, Rad Prot Dosim, 2009

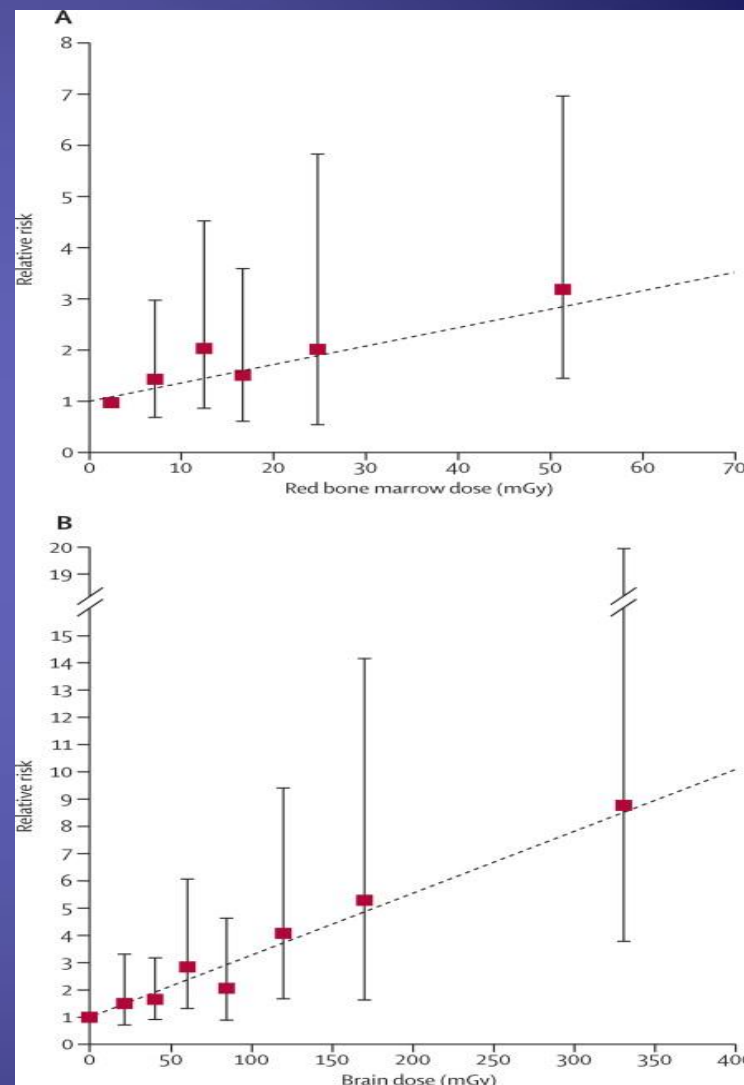- (All comparison caveats due to assumptions in effective dose, dose rate, radiation quality, etc)
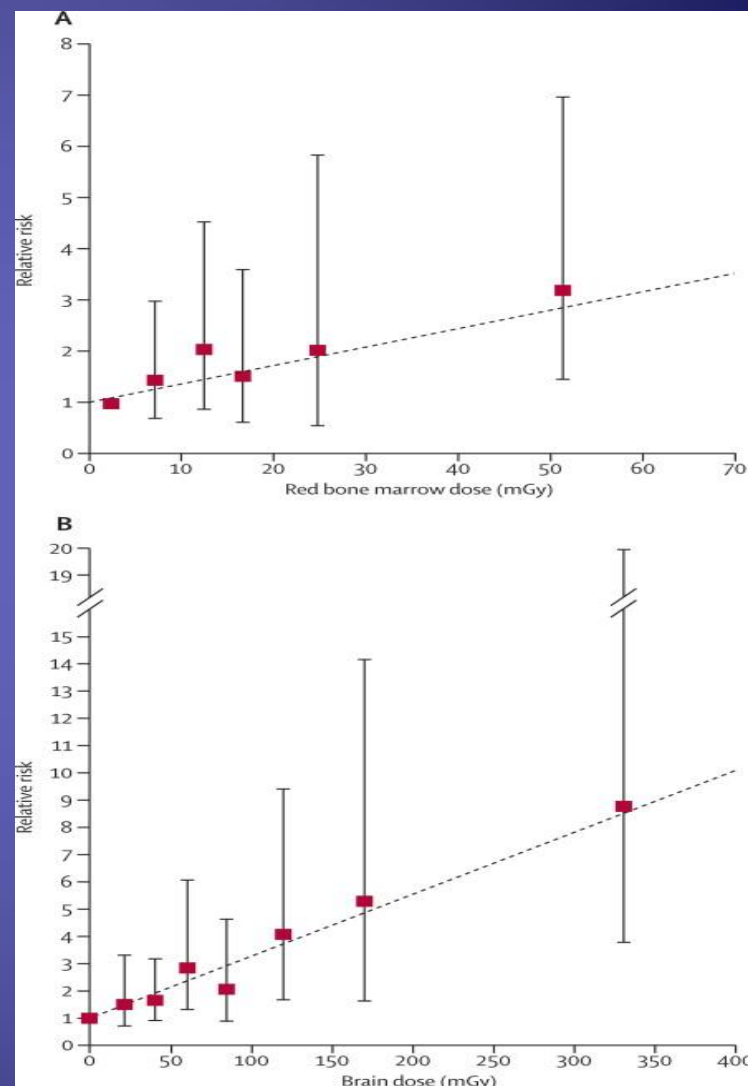
Cancer Risk from CT scans in childhood - 1

Relative risk of leukemia and brain tumors in relation to estimated radiation doses to the red bone marrow and brain from CT scans

(A) Leukemia ERR/mGy 0.036
(95% CI 0.005-0.120, p=0.01)

(A) Brain tumors, ERR/mGy 0.023
(95% CI 0.01-0.049, p < 0.0001)

Dotted line is the fitted linear dose response model (excess relative risk per mGy).   Bars show 95% CIs.

Pearce et al, Lancet, June 2012

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The cumulative absolute risks are low: one excess case of leukemia and one of brain cancer expected in the 10 years following 10,000 head CT scans performed before age 20

Pearce et al, Lancet, June 2012
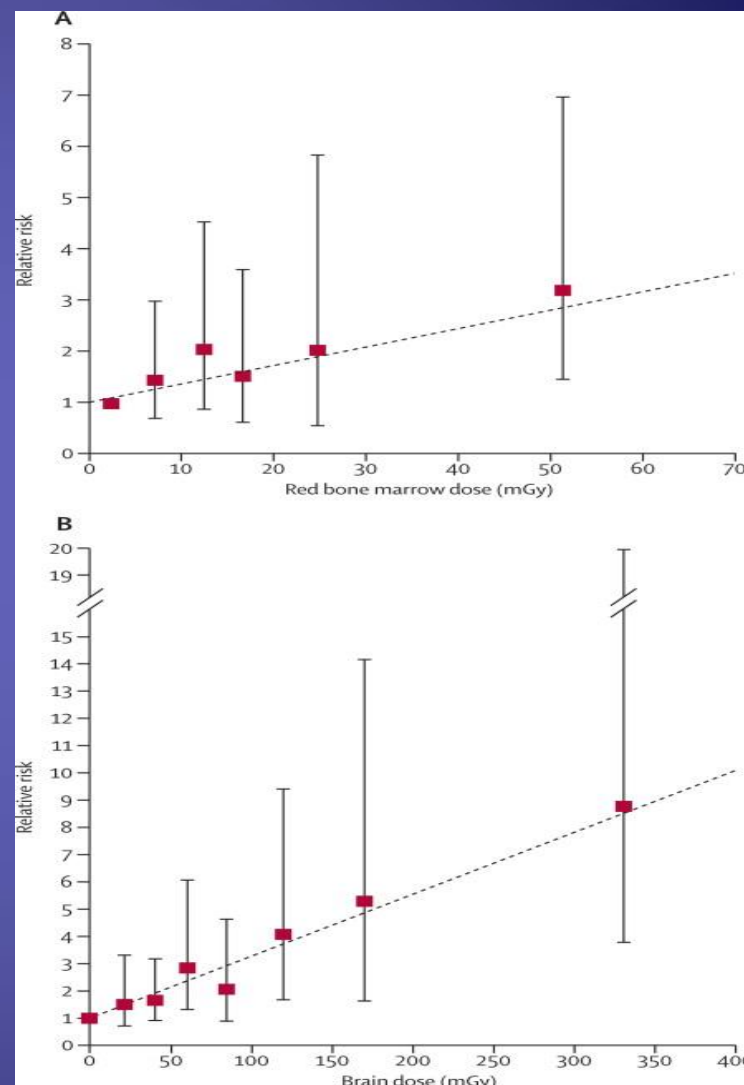
Cancer Risk from CT scans in childhood - 3

Absolute risks from CT scans are small because these cancers are relatively rare.

Benefits of CT scans can outweigh the small cumulative absolute risks.

Arguably one excess cancer is not zero; CT scan use should be clinically indicated, other tests considered, and doses kept as low as possible.

Policy and societal questions: Is the risk "worth it" for the medical benefit?

Evaluation of radiation-related health risks—is it "real"

- Is the risk in the studied group greater than expected in the general population?

- Does the risk increase with increasing radiation dose?

- Is risk related to a radiation-associated condition (e.g. breast cancer, cataracts)

- Is the increased risk consistent across studies, study designs, and populations?

- Are there biases that could explain the apparent association of health risk with radiation exposure?

Radiation studies in humans

Military

- A-bomb
- Nuclear testing
  - Atomic Vets

Environmental

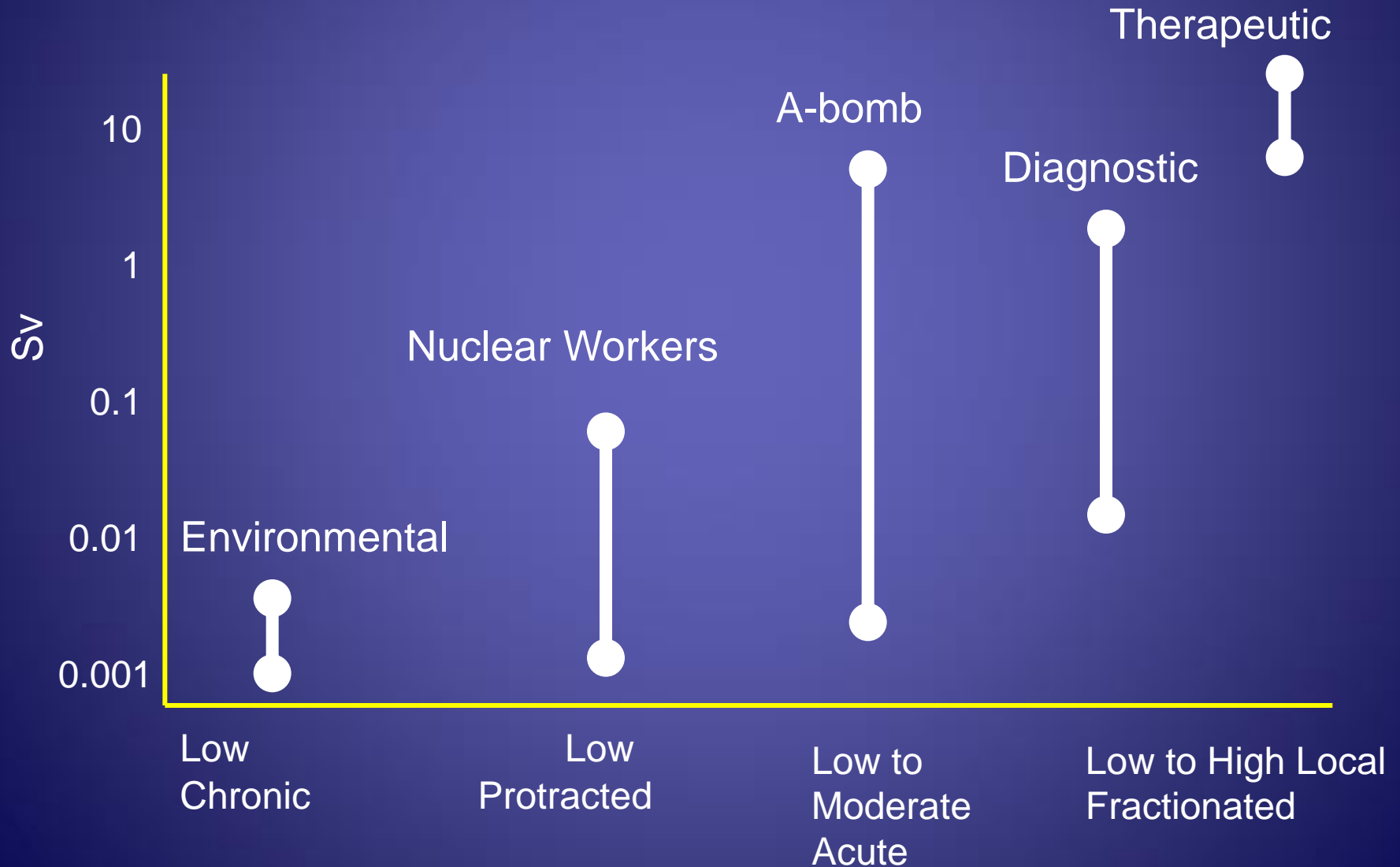- Nuclear discharges & accidents
- Radon
- Cosmic

Medical

- Diagnostic
- Therapeutic

Occupational

- Radium dial painters
- Radiologists & radiologic tech's
- Uranium miners
- Nuclear facilities

RERF Life Span Study (LSS) of Atomic Bomb Survivors

"Gold Standard"
of radiation epidemiology

Radiation Effects Research Foundation (RERF)
Hiroshima/Nagasaki, Japan

Atomic Bomb Survivors

Dose distribution, 1950-1997

Dose (Sv)	No. subjects
<0.1	69,108
0.1-1	15,363
1-2	1,613
2+	488
total	86,572

80% under 100 mSv

Preston et al, Radiat Res 2003;160:381-407

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Many incorrectly believe that the A-bomb study is a "high dose" study but the distribution by dose shows that most people were exposed to low radiation doses.
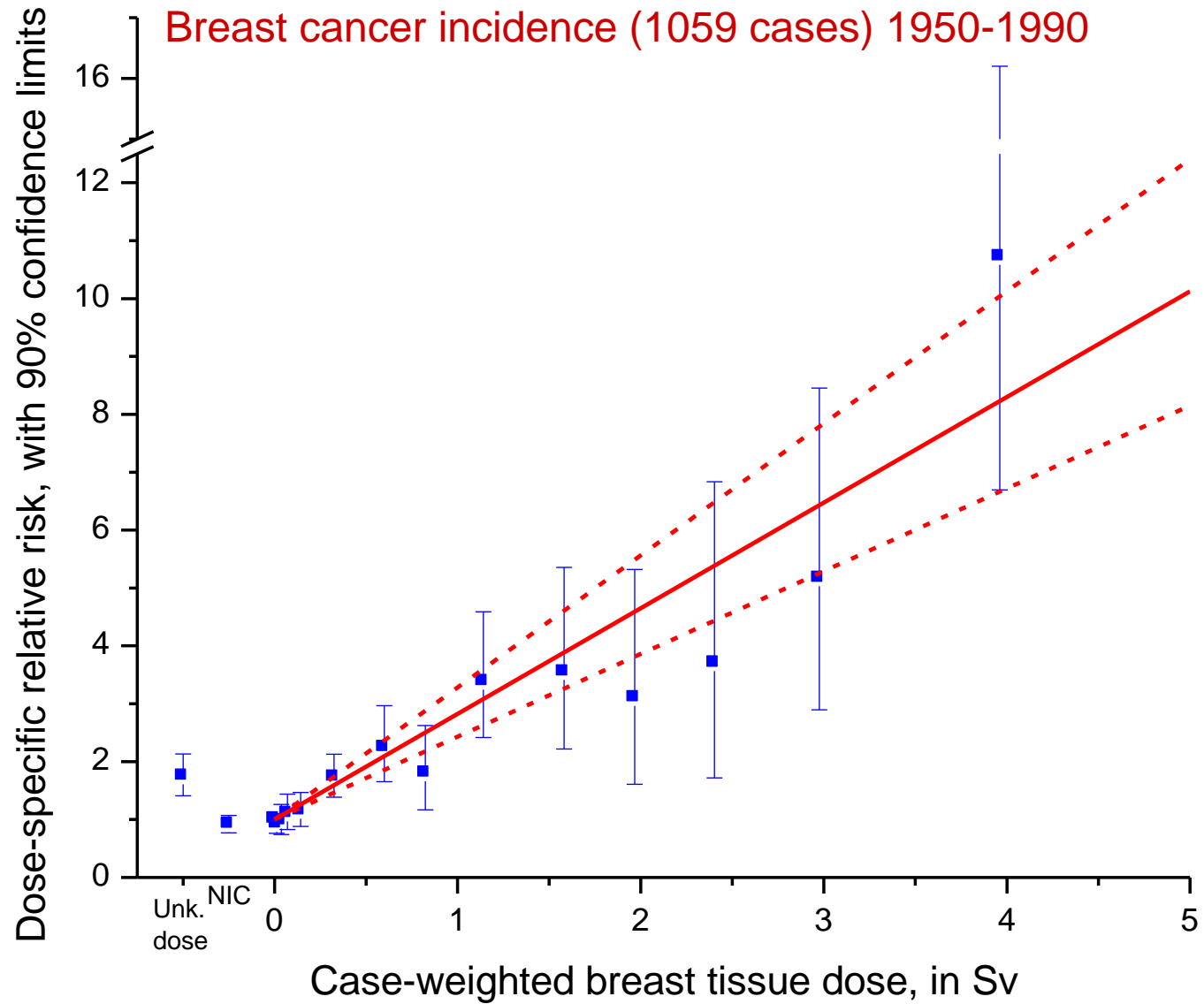
Preston et al, Radiat Res 2003;160:381-407

Atomic Bomb Survivors

Solid cancer deaths, 1950-1997

Dose (Sv)	No. subjects	All Deaths	Expected Background	Fitted Excess	
<0.1	69,108	7,110	7,065	44	<1%
0.1-1	15,363	1,869	1,635	245	
1-2	1,613	274	157	103	
2+	488	82	38	48	42%
Total	86,572	9,335	8,895	440	

Preston et al, Radiat Res 2003;160:381-407

Breast cancer incidence (1059 cases) 1950-1990

Dose-specific relative risk, with 90% confidence limits

Case-weighted breast tissue dose, in Sv

Land et al, Radiat Res 2003;160:707-717

Radiation-related breast cancer risk by age at exposure

Land et al, Radiat Res 2003;160:707-717
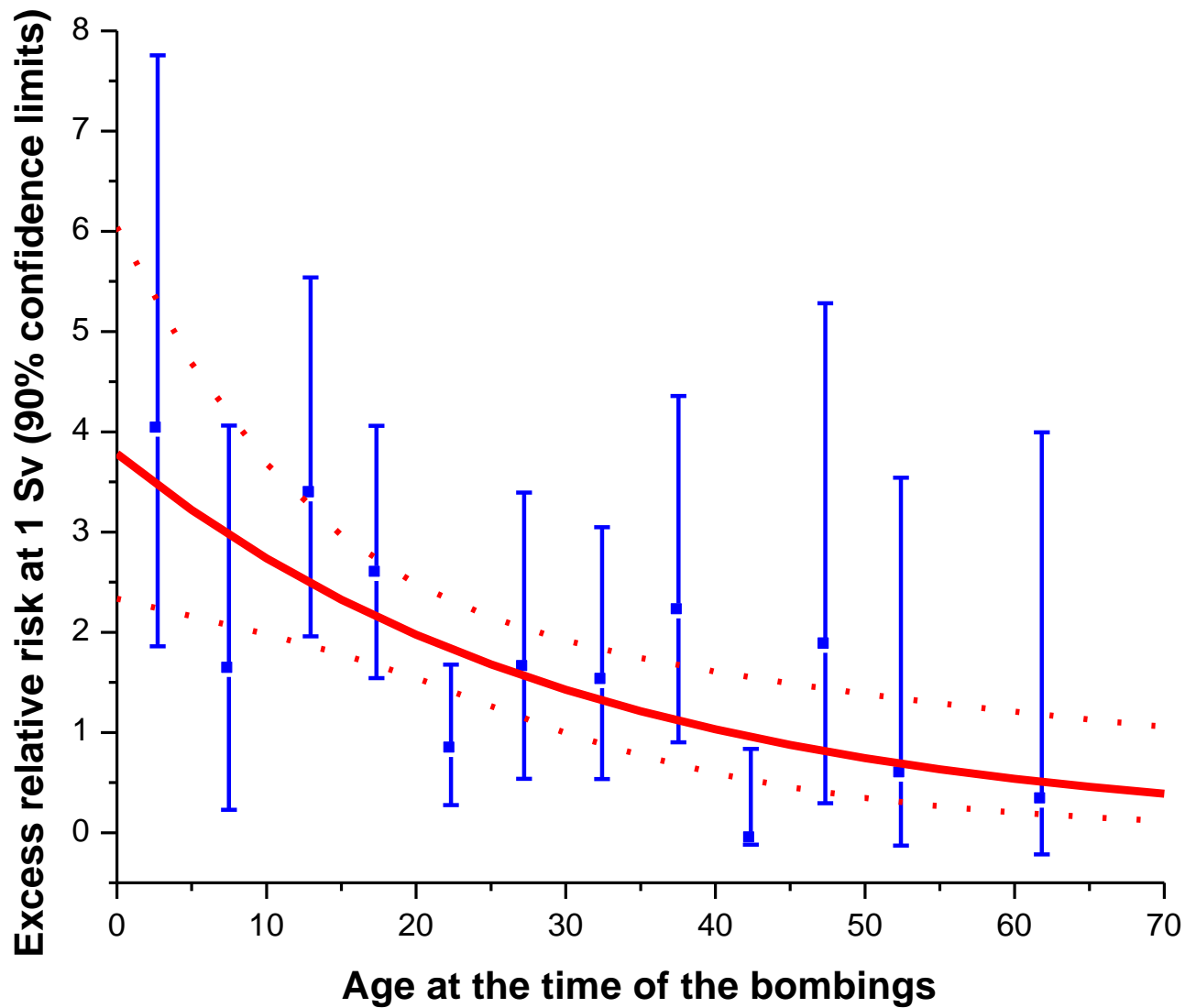
Solid Cancer Incidence Dose Response

- No evidence of non-linearity in dose response

- Statistically significant trend in

  0–0.15 Gy range

- Low dose range trend consistent with full dose range trend

ERR/Gy = 0.46 [90%CI=0.40-0.54]

Sex-averaged at age 70 for exposure at age 30
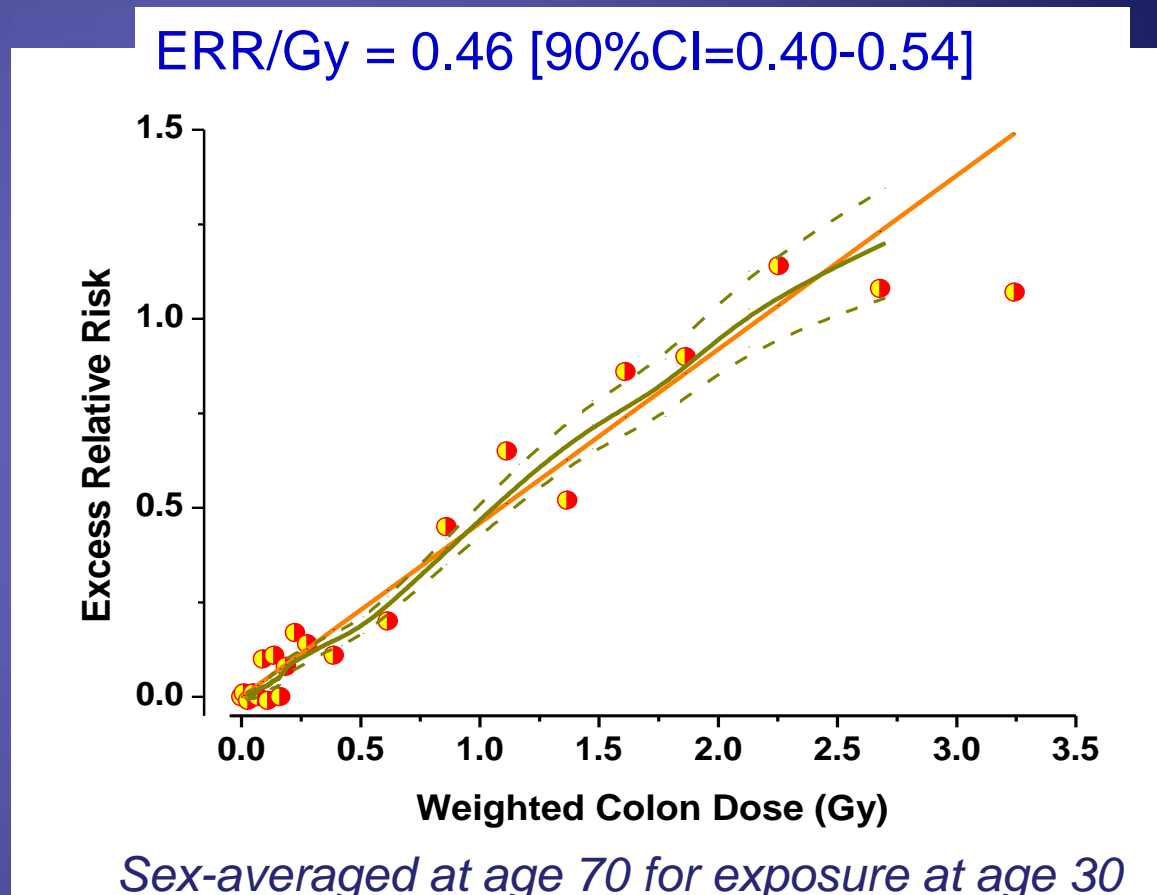
Preston et al, Radiat Res 2007

Why can't we measure risk directly at really low doses?

Say, below 10 mSv?

Lifetime risk for incidence of solid cancer and leukemia in US

If 100 people exposed to

0.1 Gy (100 mGy), expect

- 1 cancer from this exposure 🟡

- 42 cancers from other causes ⚫
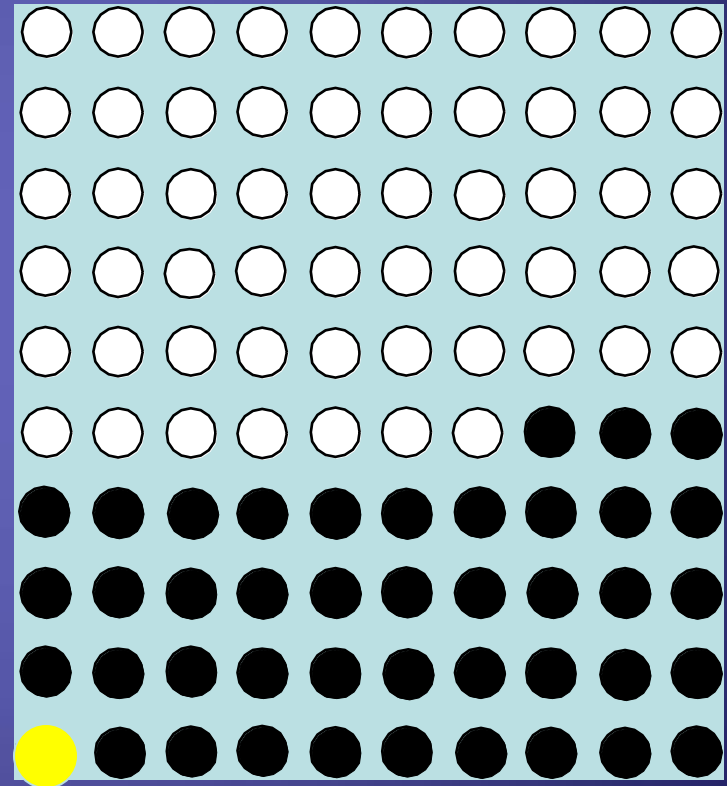
Cancer Risks from Low-dose Radiation Exposures

Difficult to Quantify Risks from Low Doses Directly

- **Infeasibly large sample size & lifetime follow-up**

Cancer risk from 2 Mammograms at age 35

60 million women & 20 years follow-up 50% power (Land, 1981)

Cancer Risks from Low-dose Radiation Exposures

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> **2 Mammograms at age 35**
>
> **60 million women & 20 years follow-up 50% power (Land, 1981)**

Estimate indirectly using existing data

- **Japanese atomic bomb survivors and others**
- **Provides a more timely assessment of potential risk**
- **Predictive models contain several assumptions**
  - **Linear no threshold, risk transfer from one population to another, dose rate, age at exposure, radiation type, etc**

Other endpoints might be used as a surrogate for risk at low doses, such as chromosome translocations.

Chromosome re-arrangements are a hallmark of malignant tumors.

Translocation detection
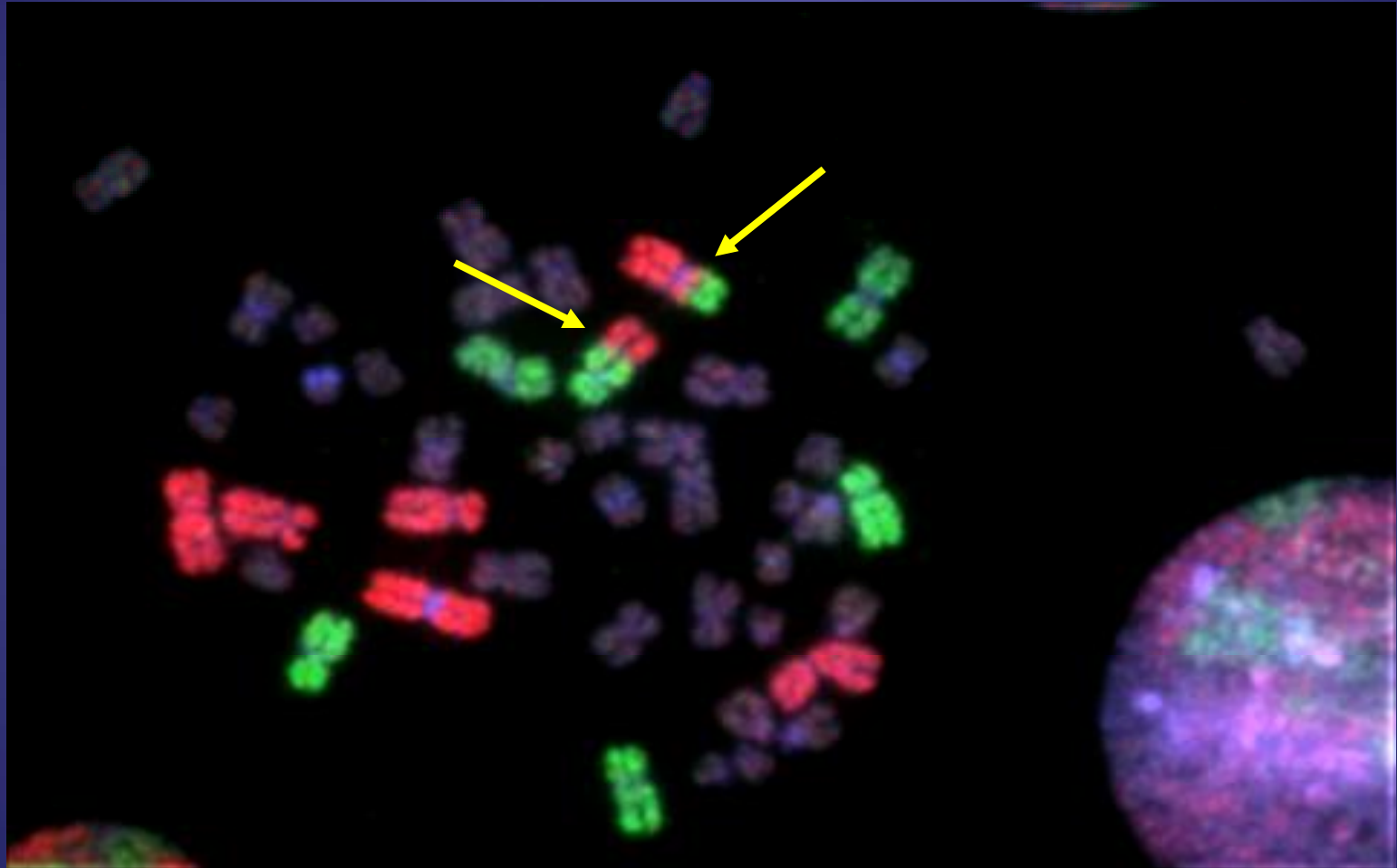
Human cell with an apparently reciprocal chromosome translocation (arrows) detected by fluorescent *in situ* hybridization (FISH) using whole chromosome paints. Chromosome pairs 1, 2, and 4 are painted red, and 3, 5, and 6 are painted green

Chromosome translocations in airline pilots

- Translocations increased with years of flying

  – 83 pilots (mean age 47)

  – Average flight years was 18 (range 1-37 years)

  – Average 5 years with international flights

  – Adjusted for age, diagnostic medical radiation exposure, and military flying

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Yong et al, Occupational Environmental Medicine, 2009

What do some of the recent air crew studies

of cancer risk show?

Studies in airline pilots, flight crew, air traffic control officers

- Overwhelming healthy worker effect
  - Reduced risk of all cancers, overall mortality, and markedly lower cardiovascular disease
- Specific cancer sites elevated
  - Brain (pilots), breast (flight attendants), melanoma (all groups)
- Real risk relationships unlikely
  - No dose response for brain tumors
  - Melanoma related to host factors
    - Skin, hair color (dos Santos Silva et al, Int J Cancer, 2013)
  - Reproductive factors explain some breast cancer risk (but not all); risks inconsistent across all studies

# Studies in airline pilots, flight crew, air traffic control officers

- Review of all studies since 1990 (n=65)
  - Mortality from cancer and other causes
  - Cancer incidence
    - Hammer et al, Radiat Prot Dosim, 2009
- General summary
  - Zeeb et al, J Radiol Prot, 2012
- Focus on preventable deaths?
  - 3-fold Increased mortality from alcoholism, drowning (alcohol related), intentional self-harm

----Pinkerton et al, Pan Am flight attendant cohort, 2012

Summary

- Ionizing radiation is a known carcinogen

- Cancer risk decreases as dose decreases

- Excess absolute risk at low doses is minimal, but it is not zero
  - Exact risk, based on human studies, will never be known
  - Model projections could estimate absolute risk with uncertainties for airline crews, frequent fliers

- Airline pilots and crew unique occupational group

- Risk vs Benefit:
  - Int'l Air Transport Association estimated 1.8 billion passengers flew in 2010; 40% international flights

- High dose space weather events likely call for prudent avoidance to reduce unnecessary exposure

The End

"And it was so typically brilliant of you to have invited an epidemiologist."
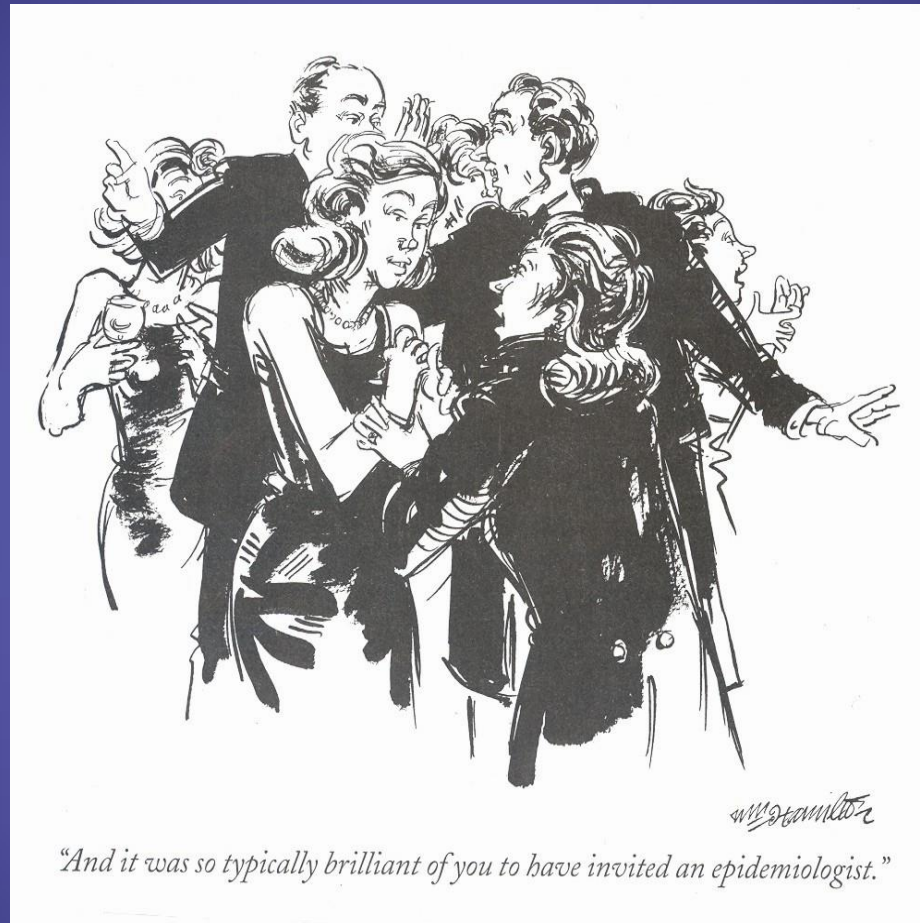
Hopefully it was true!!!! Thanks for the invitation!

# Translocation rate by occupational radiation absorbed dose to RBM among US Radiologic Technologists

Slope for occupational red bone marrow dose (continuous):
p = 0.02
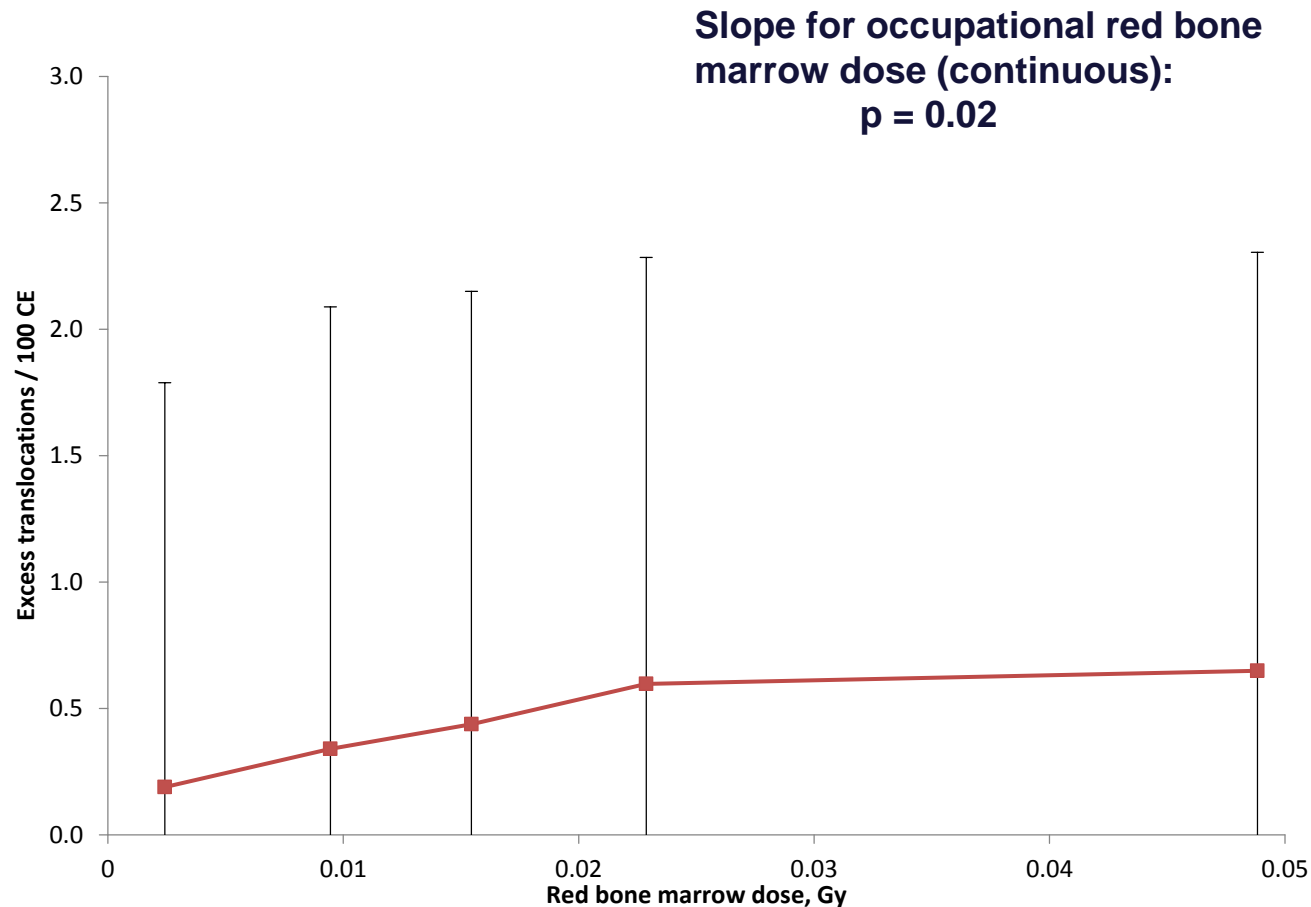
Slope for personal diagnostic medical exposures (continuous, P < 0.0001) was the same as for occupational dose

Excess chromosome aberrations with respect to the background rate, with 95% CI (adjusted for overdispersion), in the combined biodosimetry effort data for quintiles of occupational dose, here shown for under 50 mGy.
Background rate is adjusted for age, sex, and study group.   Little et al, in press, Radiation Research

Chromosome translocations associated with diagnostic medical radiation in radiologic technologists, airline pilots, and faculty
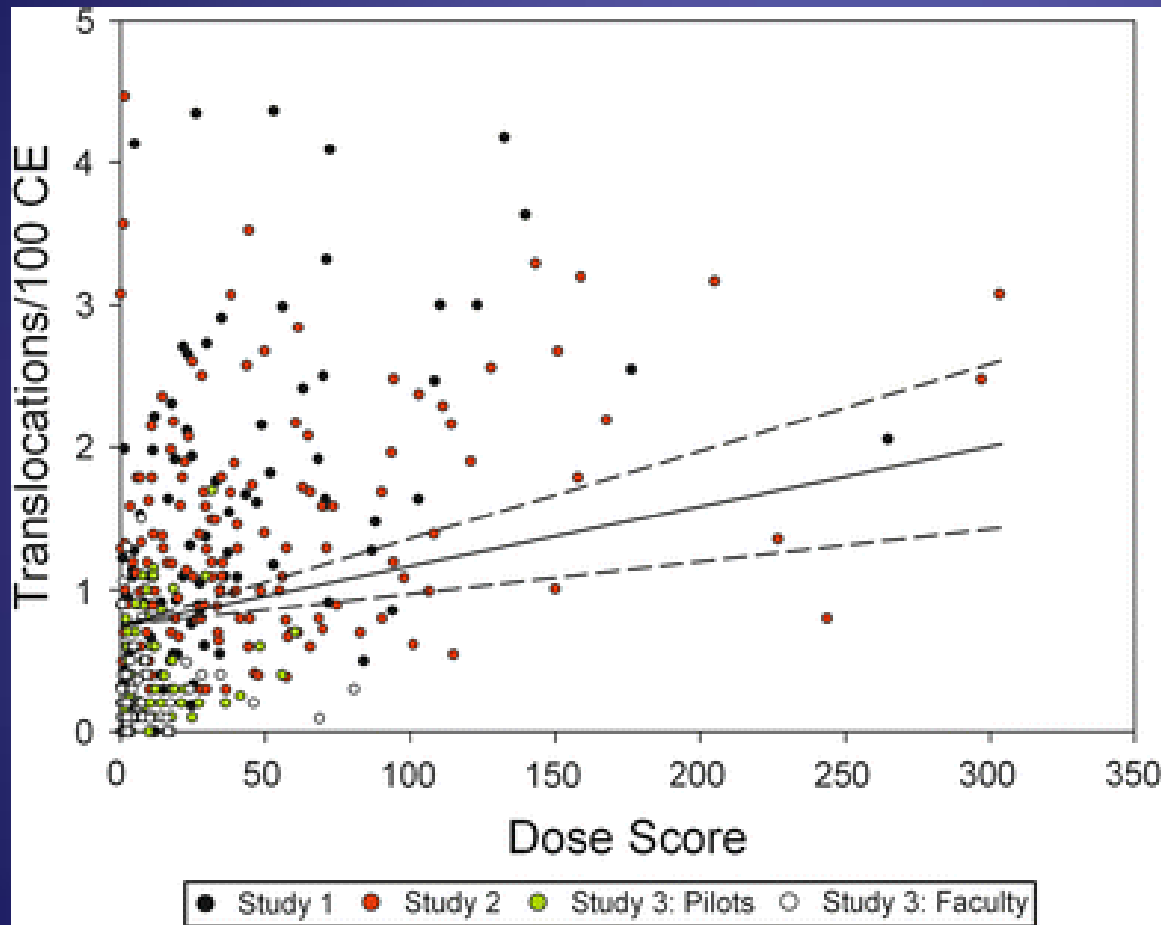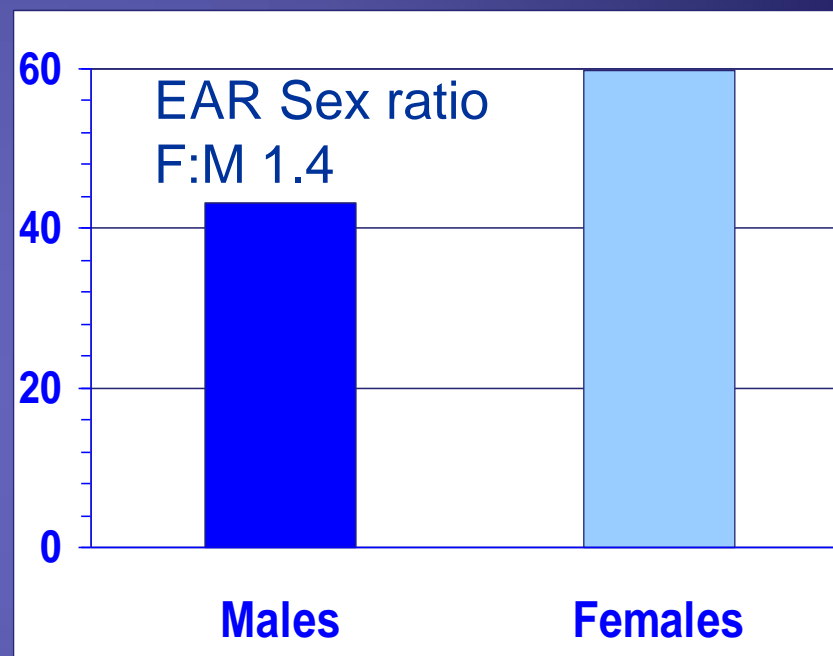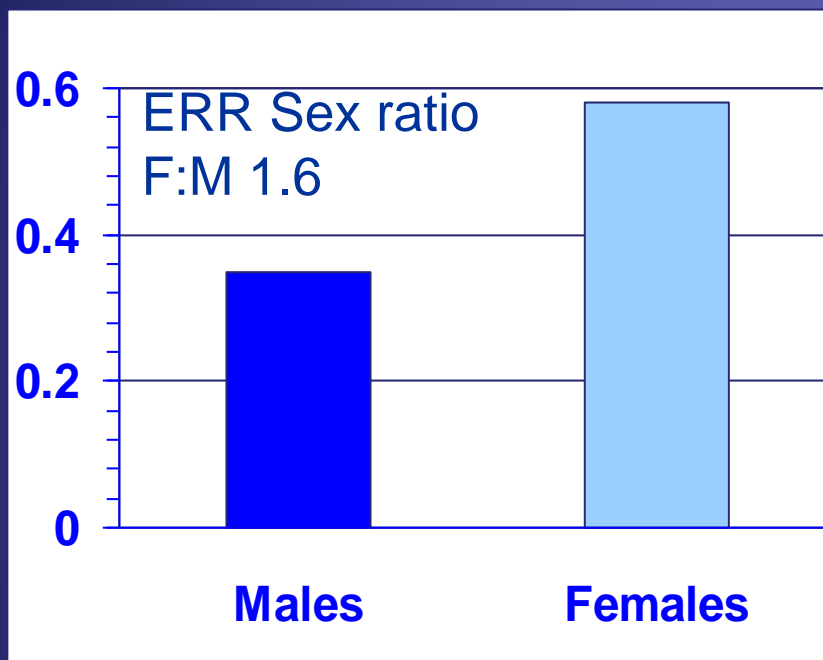

Diagnostic X-ray examinations and increased chromosome translocations: evidence from three studies

Bhatti et al, Radiat Environ Biophysics 2010

Translocation frequency as a function of the cumulative diagnostic red bone marrow radiation dose score (n = 362).   The trend line with 95% upper and lower confidence bounds is from multivariable Poisson regression analysis [0.04 excess translocations/100 CE/10 bone marrow dose score units (95% CI: 0.02, 0.06; P < 0.001); R^2 = 0.7]. Dose score approximates mGy.
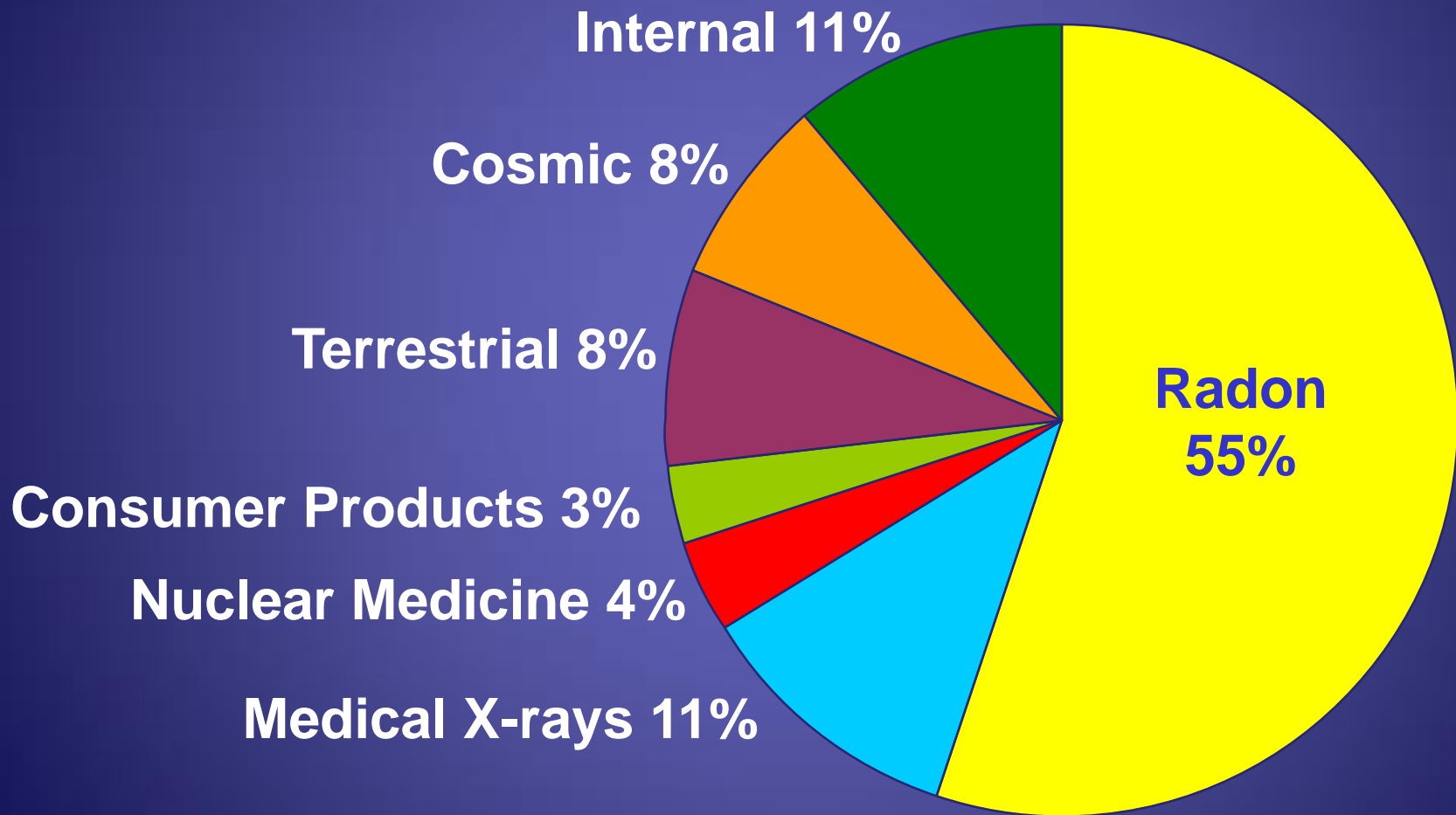
Solid Cancer Risks by Gender

ERR Sex ratio
F:M 1.6

0.6	
0.4	
0.2	
0	

Males   Females

EAR Sex ratio
F:M 1.4

60	
40	
20	
0	

Males   Females

For person age 70 exposed at age 30

Preston et al, Radiat Res 2007

Sources of Ionizing Radiation

Internal 11%

Cosmic 8%

Terrestrial 8%

Consumer Products 3%

Nuclear Medicine 4%

Medical X-rays 11%

Radon 55%

Increase in Medical Sources of Radiation Exposure in the U.S.

1980

0.5mSv **<0.1mSv**

Other
Natural background

3mSv
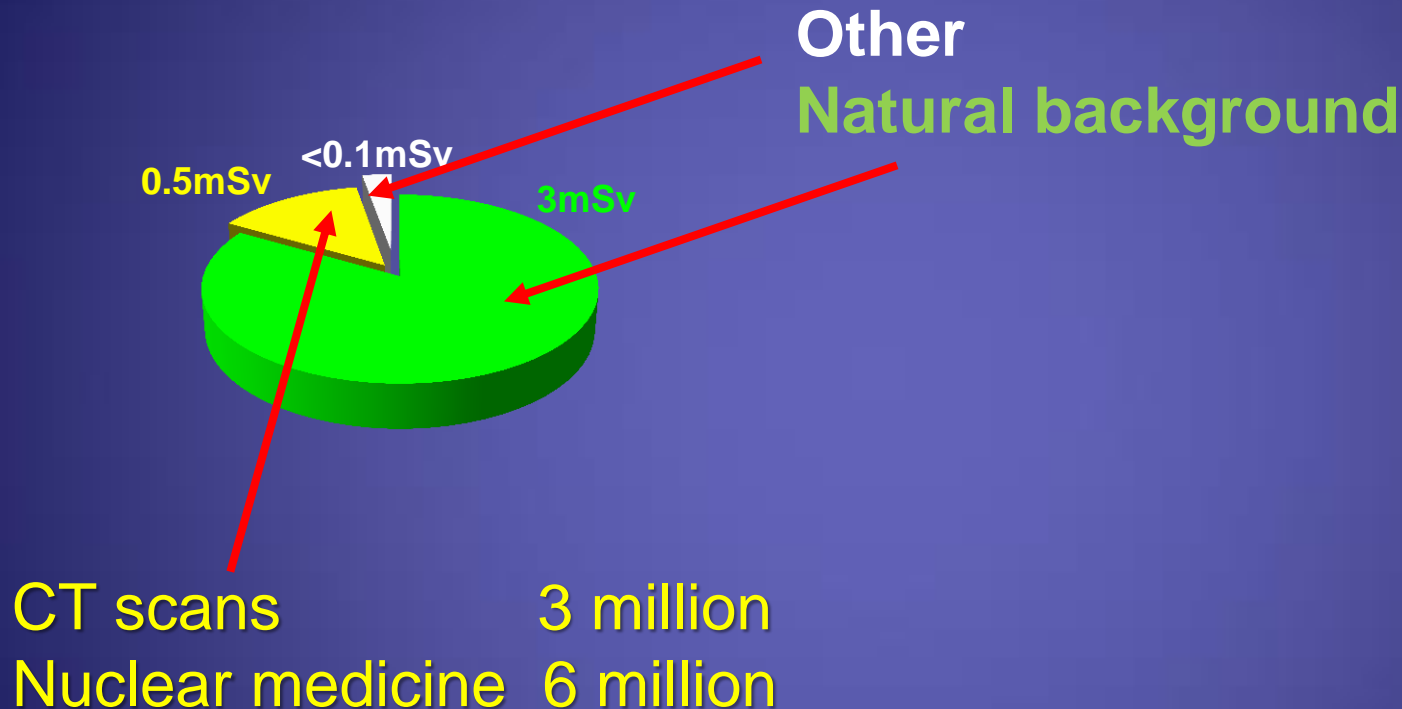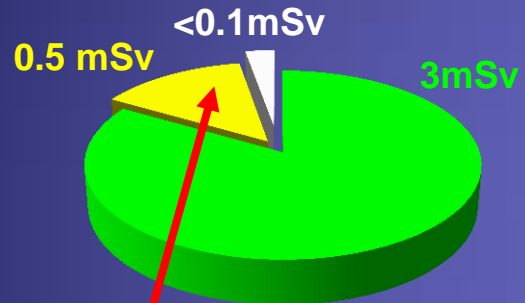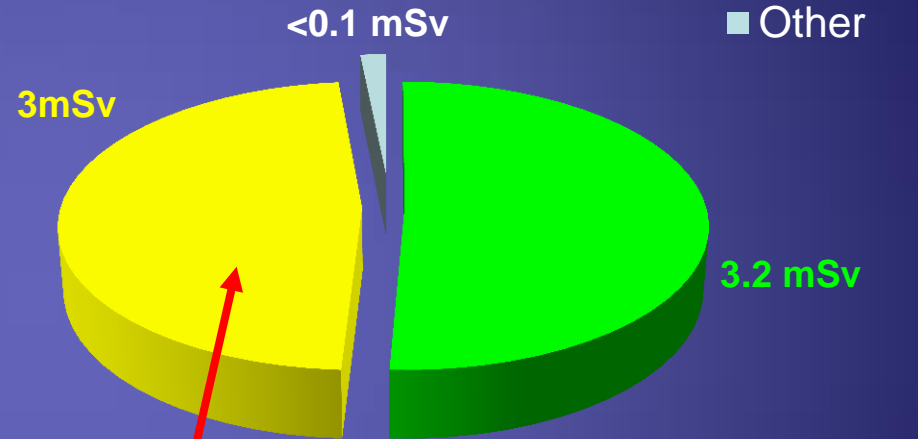
CT scans   3 million
Nuclear medicine 6 million

Increase in Medical Sources of Radiation Exposure in the U.S.
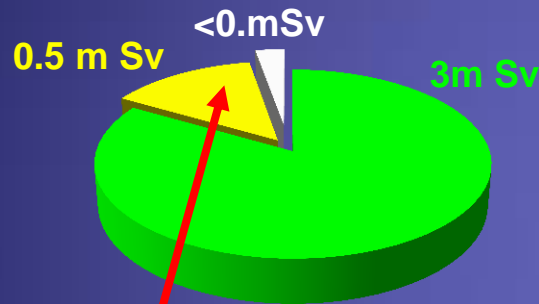
1980

2006

Natural
Medical
Other

<0.1mSv
0.5 mSv
3mSv

<0.1 mSv
3mSv
3.2 mSv

CT scans   3 million
Nuclear medicine 6 million

CT scans   70 million
Nuclear medicine 18 million

Slide courtesy of Dr. Amy Berrington de Gonzalez

Increase in Medical Sources of Radiation Exposure in the U.S.

1980

2006

■ Natural
■ Medical
■ Other

0.5 m Sv

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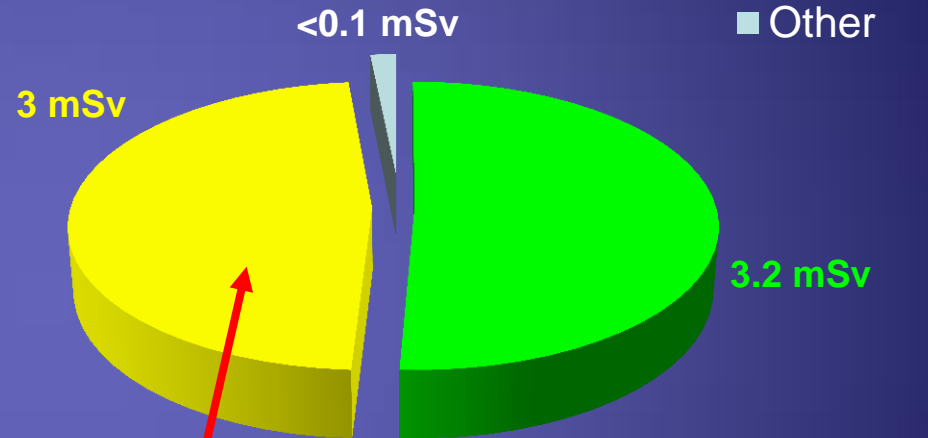
CT scans   70 million
Nuclear medicine 18 million

Population exposure to medical radiation sources has increased _six-fold_ in the last two decades!

Comparing Radiation Doses

| Activity	Level
US Average, all sources	3-6 mSv per year
Fallout	0.005 mSv per year
Cosmic rays on earth	0.26 mSv per year
Cosmic radiation to flight crew	0.2-5.0 mSv per yr
Chest x-ray	~0.1 mSv
Mammogram (breast)	~3 mSv [↑ RBE?]
A-bomb (median whole body)	<100 mSv
Cancer treatment (tumor)	10,000–70,000 mSv

Key analytic aspects

- Quantitative estimation of radiation exposure
  - Dosimetry
  - Formal understanding of uncertainty in dose

- Linear dose-response (few exceptions--leukemia)
  - RR = $1+\beta*dose$

- β = Excess Relative Risk (ERR) per unit dose
  - ERR/Gy = RR-1
  - Usually per one Gy but depends
  - ERR significant if the 95% CI excludes zero

Life Span Study (LSS) Cohort

- Survivors within 2.5 km of the bombings (0.005-4Gy)

- Survivors within 2.5-10 km

- Not-in-city (NIC)

  TOTAL PEOPLE   120,321

- Hiroshima and Nagasaki tumor registries (1958-98)

- 17,448 first primary tumors

- DS02 organ dose estimates

Preston et al. Radiat Res, 2007
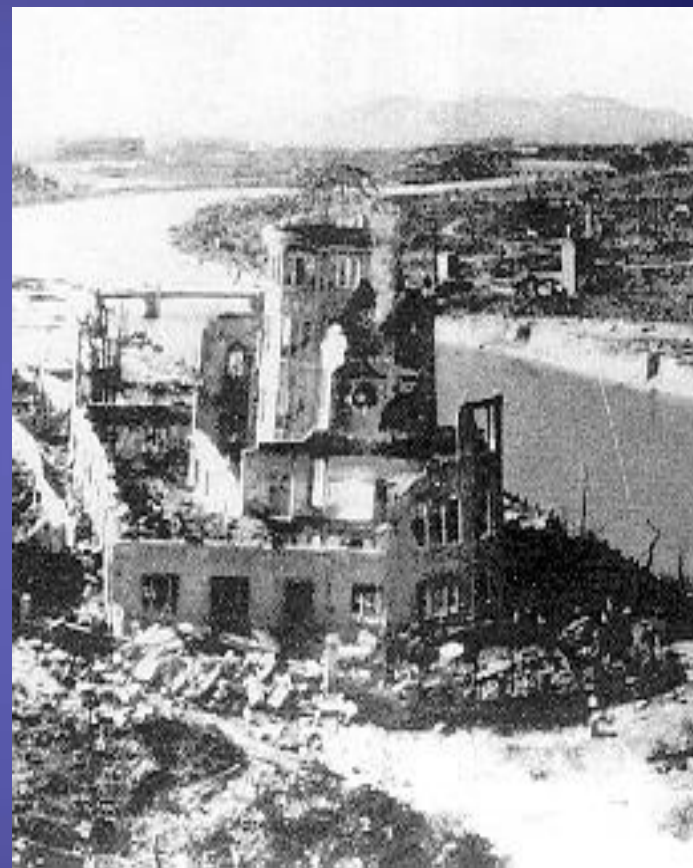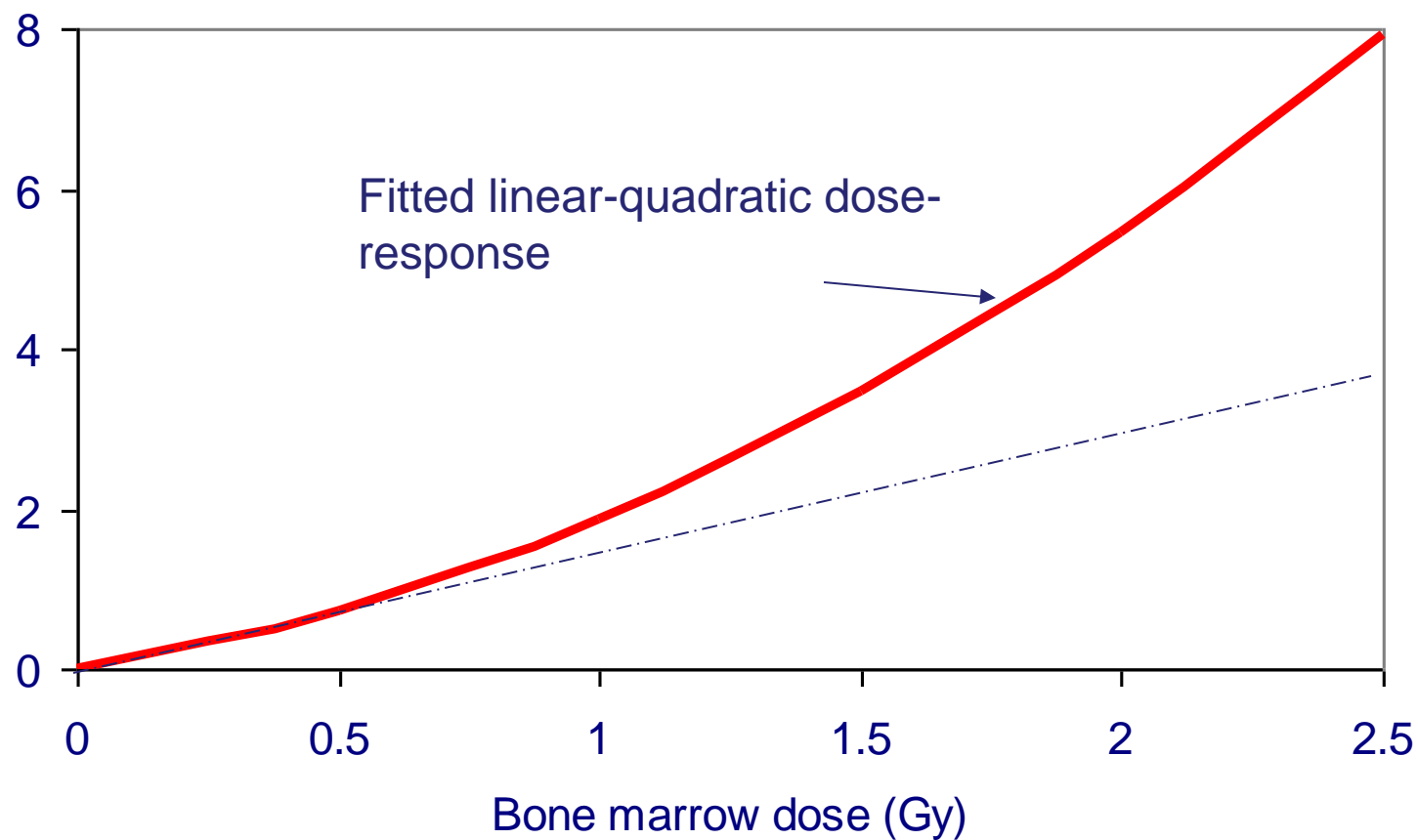
LSS Cancer Incidence Cohort

Dose (Gy)	Person Years	Subjects	%
Not in city	680,744	25,247	23.9
< 0.005 in city	918,200	35,545	33.7
0.005 - 0.1	729,603	27,789	26.4
0.1 - 0.2	145,925	5,527	5.2
0.2 - 0.5	153,886	5,935	5.6
0.5 - 1	81,251	3,173	3.0
1-2	41,412	1,647	1.6
2+	13,711	564	0.5

Preston et al, Radiat Res 2007

Solid Cancer Temporal Patterns
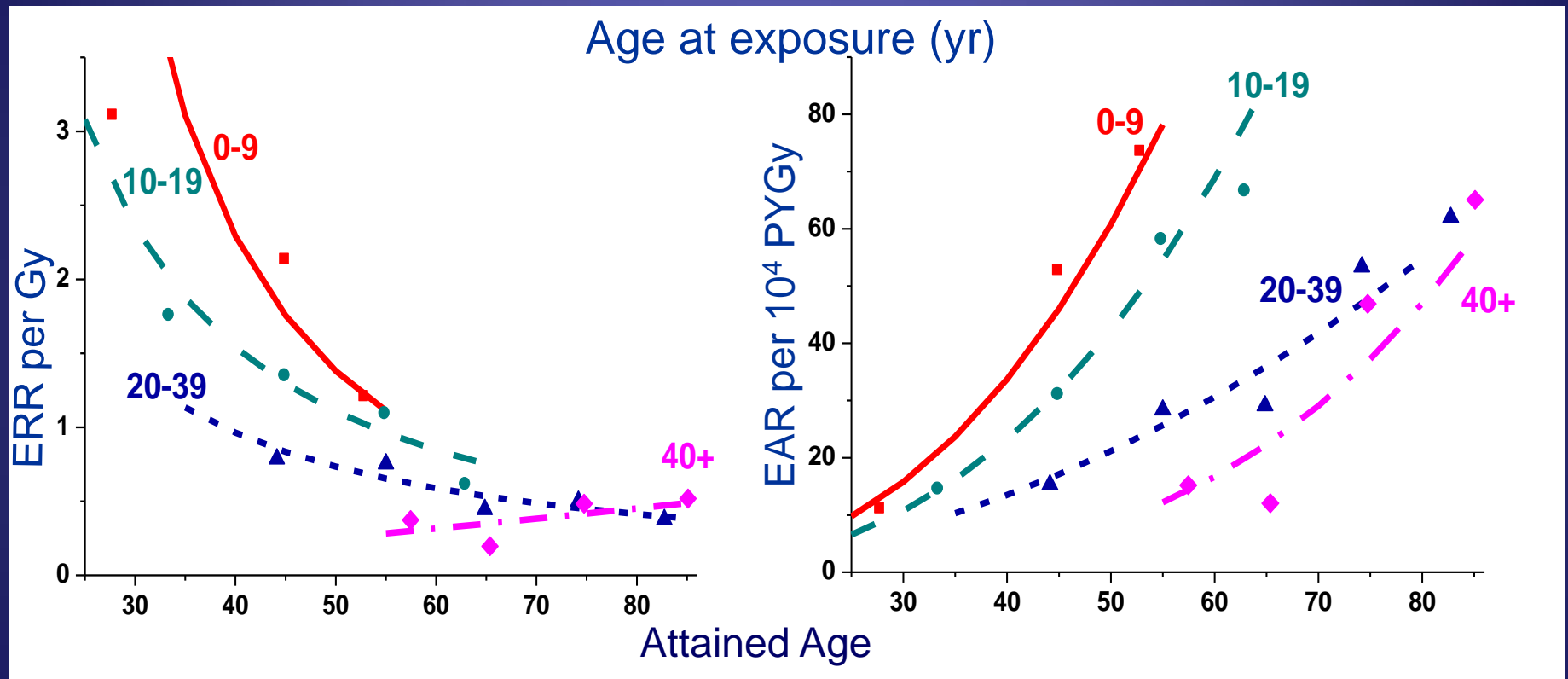
Preston et al, Radiat Res 2007

ERR per Gy for leukemia incidence
(BEIR VII model)

Fitted linear-quadratic dose-response

Bone marrow dose (Gy)

Sex-averaged at age 70 for exposure at age 30

BEIR VII, 2006

Site–Specific Cancer Risk Estimates
ERR at age 70 for exposure at age 30
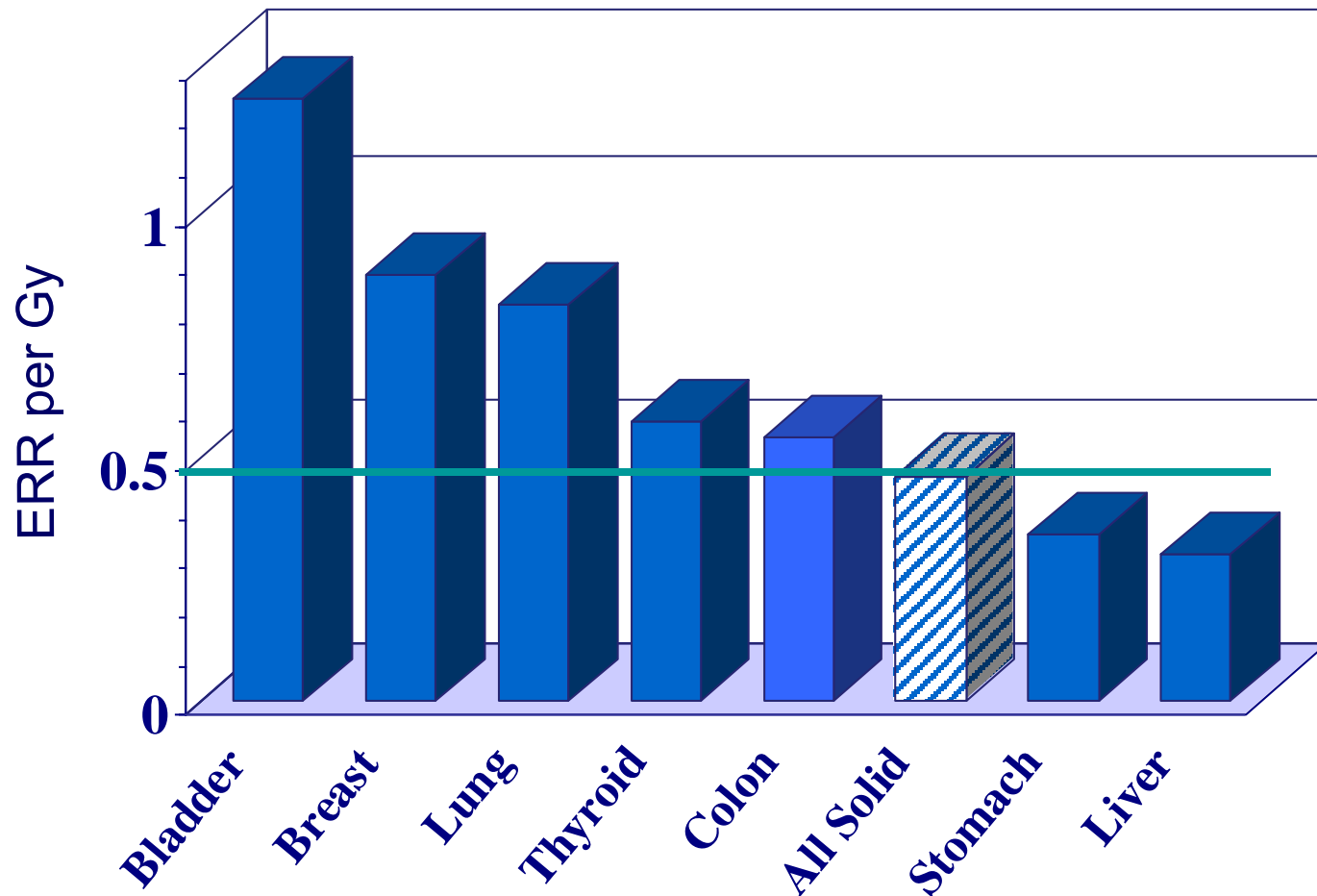
Preston et al, Radiat Res 2007

Summary LSS

- Solid cancer incidence data
  - Linear dose-response with no threshold
  - Excess risk continues throughout life
  - Risks vary with age
  - Some variation by cancer site

- Leukemia
  - Linear quadratic dose-response
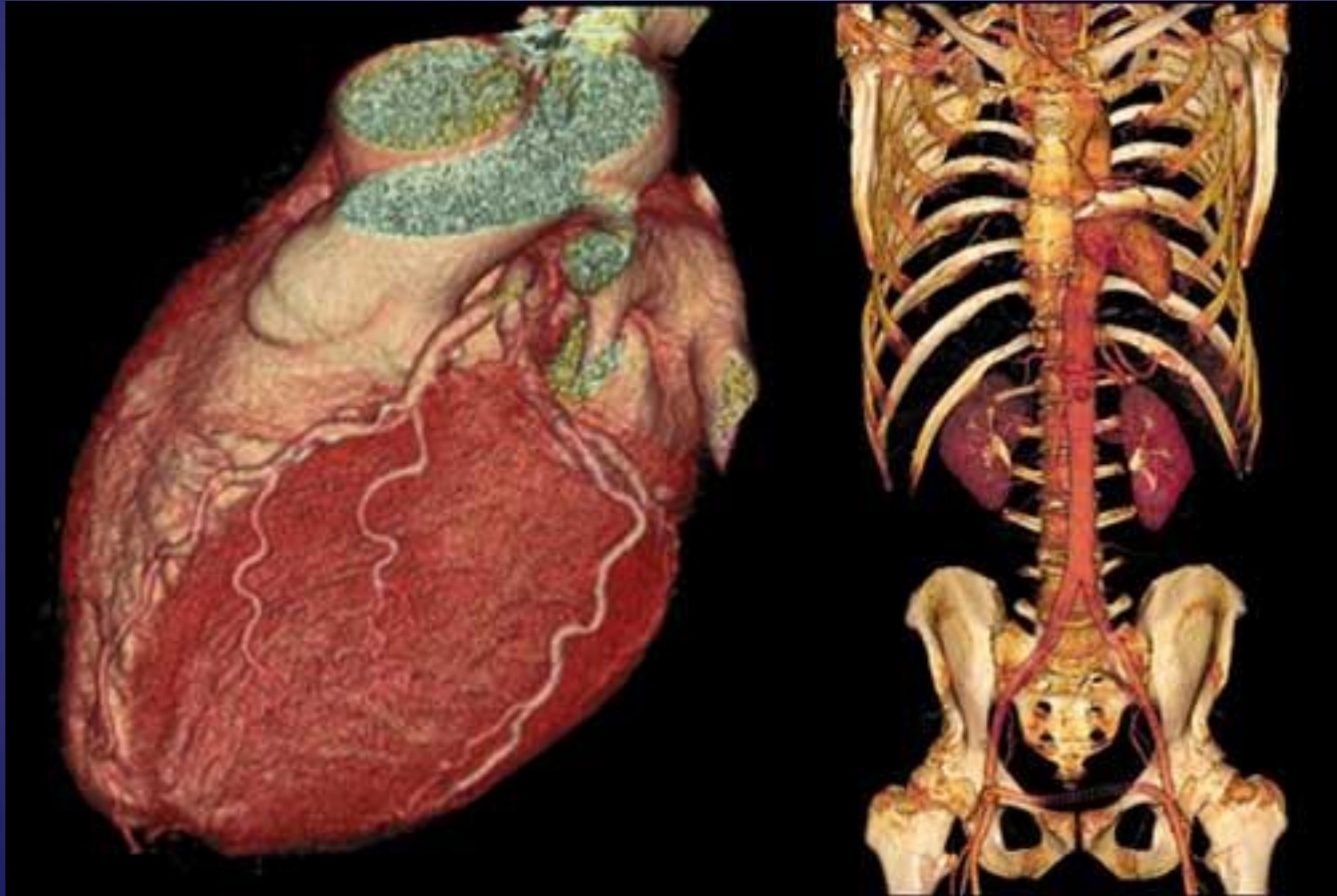
Strengths of LSS Cohort

- Large, healthy non-selected population

- All ages and both sexes

- Wide range of well characterized dose estimates

- Mortality follow-up virtually complete

- Complete cancer ascertainment in tumor registry catchment areas

- More than 50 years of follow-up

Limitations of LSS Cancer Incidence Data

- Inadequate solid cancer data from 1945-1958 and no leukemia data from 1945-1950

- Cancer patterns different in Japanese

  – Eg stomach and liver cancer common

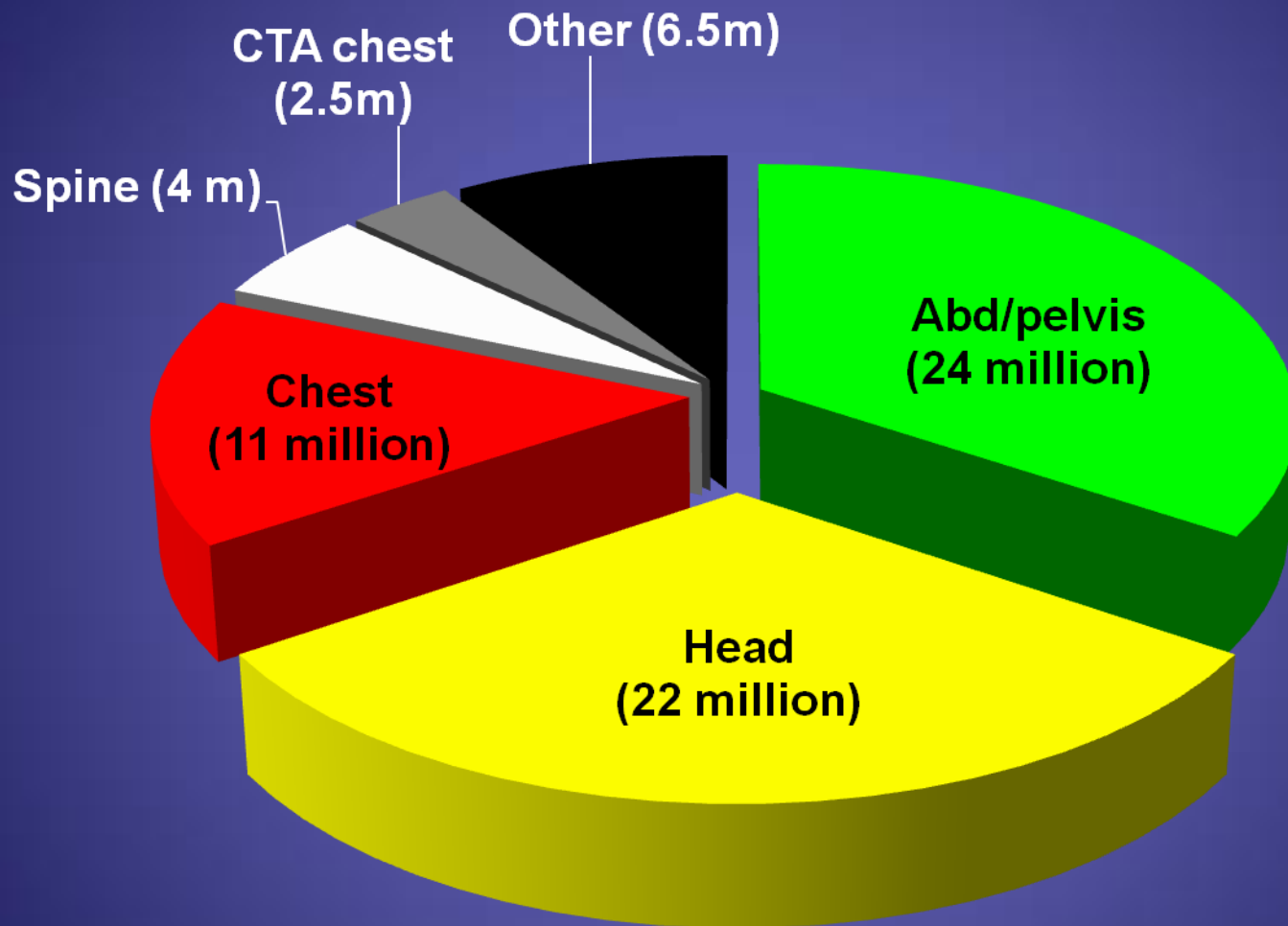 – Breast and prostate cancer less common

- Single acute exposure

CT Scans
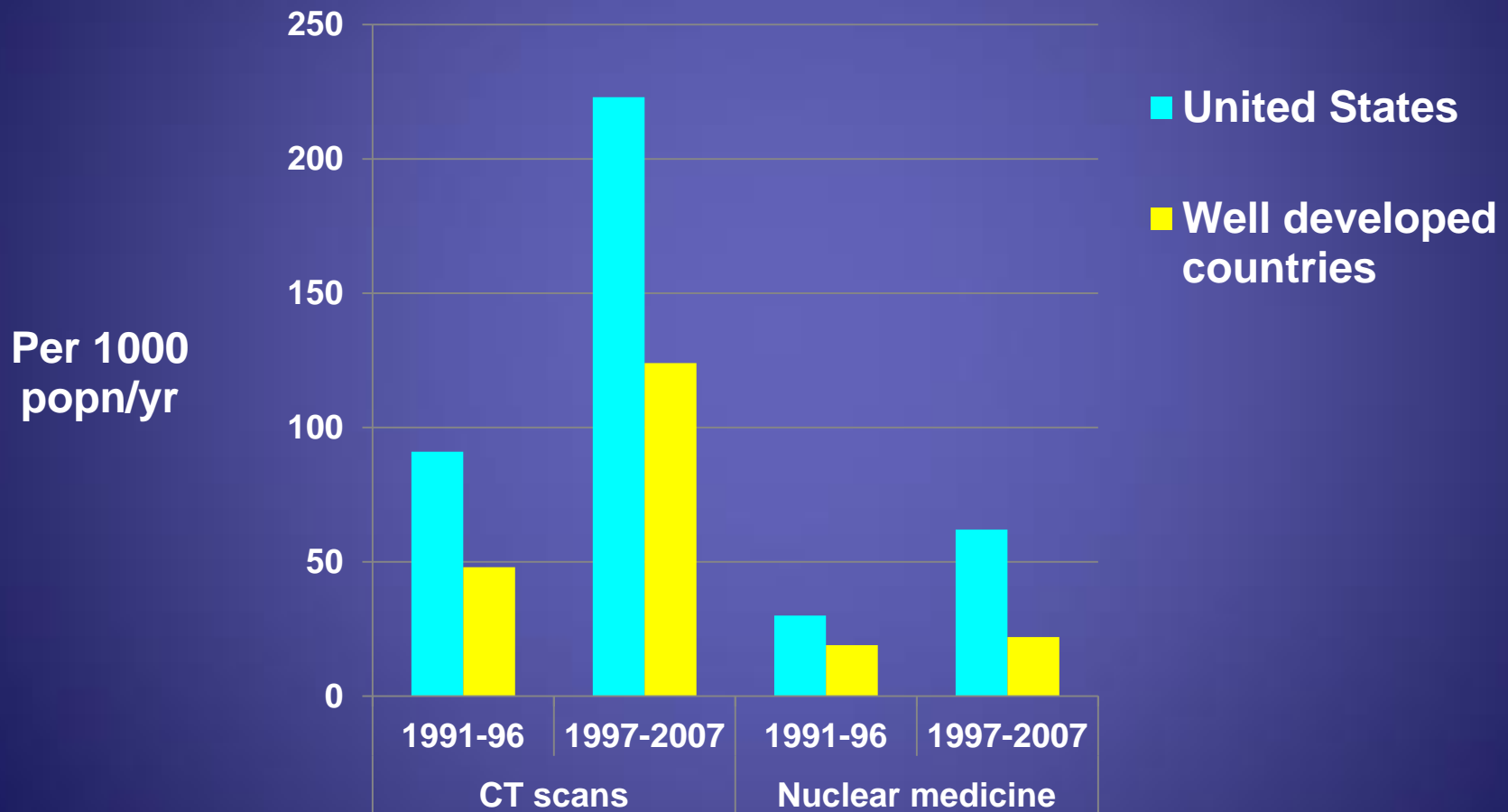
70 Million CT scans U.S. 2007

CTA chest (2.5m)

Other (6.5m)

Spine (4 m)

Abd/pelvis (24 million)

Chest (11 million)

Head (22 million)

Slide courtesy of Dr. Amy Berrington de Gonzalez

Mettler F et al (Radiology 2008); IMV 2008

International Trends in Diagnostic Imaging

Per 1000 popn/yr

Legend: ■ United States ■ Well developed countries

Categories: CT scans (1991-96, 1997-2007), Nuclear medicine (1991-96, 1997-2007)

Mettler F et al (Radiology 2009)

Slide courtesy of Dr. Amy Berrington de Gonzalez

Cancer Risk from CT scans in childhood - 3

Study has been criticized because:

-Reason for scan not collected
- Could be reverse causation
- Indolent brain tumor causes an accident for which a CT scan is ordered
- Risk for brain tumor appears spuriously elevated

-Underlying conditions such as Downs Syndrome are associated with more scans
- Downs Syndrome children at higher risk for myelodysplasias
- Risk for leukemia appears spuriously elevated when myelodysplasias included

-Brain tumor risk increased with age at exposure rather than decreased

Dr. Mark Pearce et al, Lancet, June 2012
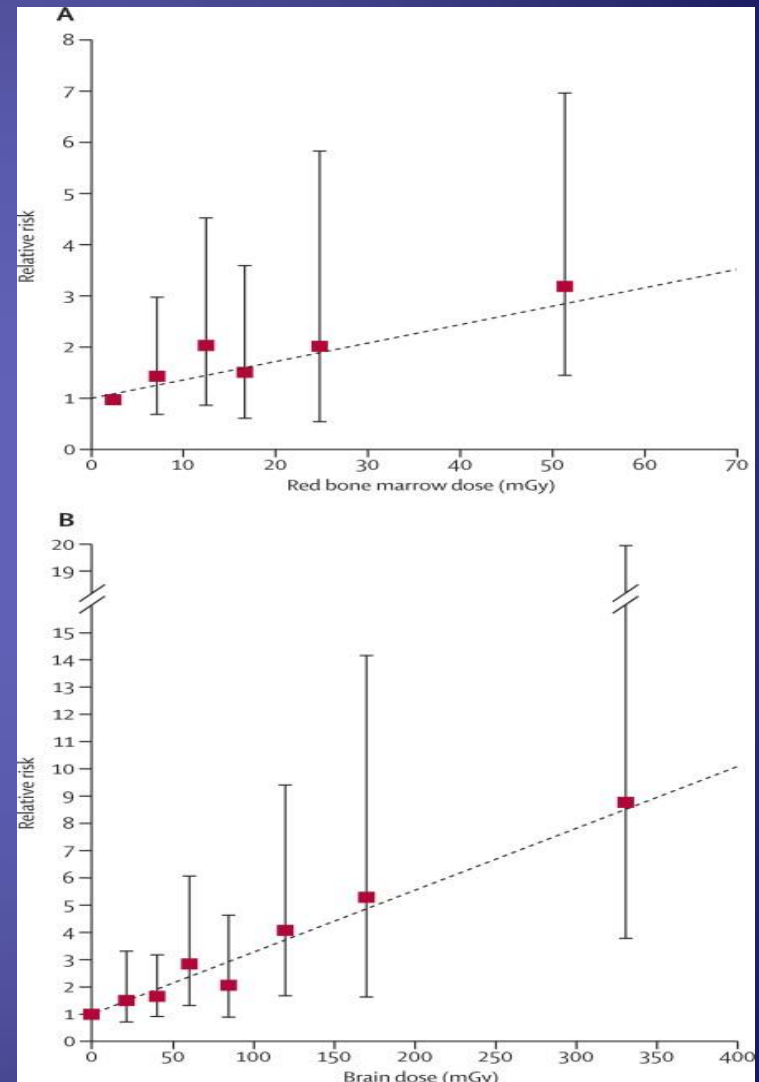
Summary

- Ionizing radiation is a weak carcinogen

- Carcinogenicity shown beyond doubt

- Good exposure assessment required

- Shape of dose response well established for many different cancer sites

- Promising to study gene-environment interactions (e.g., DNA repair, apoptosis genes) and interaction with polygenes (multiple genes/variants combined)

- Late effects of low-dose radiation remain controversial --- statistical power